Nephrolithiasisin pediatrics: A literature review

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Abstract
Background: Despitehaving a higherprevalence in adults, theincidenceofnephrolithiasisisobservedatthesame time in pediatricpatients, constitutinganimportant cause ofchildhospitalization. The possibilityofprogressiontochronickidneydisease in thelongterm, ifthediagnosisandtreatment are notperformedcorrectly, indicatesthepotentialseverityofthisdisease.
MaterialsandMethods: Thispaperconducted a literaturereview non-systematic. The electronicdatabasesPubmedandScielowereused. Onlyarticles in Englishlanguagewassearched. For thelocationofthearticles, theterms"pediatric", "nephrolithiasis", "stones", "pediatric" and "children" wereapplied.
Results: articlespublished from 2010 to 2020 wereprioritized. In addition, themostrelevantworkswereincluded, accordingtotherespectivedatabases. In all, 47 sourceswereselected.
Conclusion: The presentationanddevelopmentofthenephrolithiasis in children,although similar totheadultdisease, presentspeculiarities, beingimportant its knowledge, toobtainadequate management ofthepatientandavoid future complications.
Keywords: Nephrolithiasis; Child; kidneydiseases; abdominal pain; diagnosis.

I.   Introduction

Lithiasis or urinary calculus refers to the presence of one or more stones inside the urinary tract, resulting from biomineralization processes of substances such as calcium, citrate, oxalate, and uric acid. Despite having a higher prevalence in adults, the increasing incidence of nephrolithiasis is observed at the same time in pediatric patients, constituting an important risk of morbidity, since it may culminate in recurrent pain episodes, the need for hospitalizations and invasive procedures until progression to chronic kidney disease (CKD).[1,2,3]

It is not clear the Brazilian prevalence of urinary calculus in children, and most of the cases refer totheworld population.The incidence of 1 to 2.7% of nephrolithiasis in pediatric patients is estimated and is, therefore, a relatively uncommon entity.[4,5]However, there is a worrying increase in this statistic, estimated at 4-10% annually, in the last two decades.[3] Studies indicate 6-10% increase in the annual incidence of the disease in the United States, especially between 15 and 19 years of age.[1]It is estimated that 50 out of every 100,000 adolescentshave kidney stones.The current mean age for the first episode of nephrolithiasis is 4.4 years in boys and 7.3 years in girls.[4,5]This growth is attributed to the precariousness of eating habits, with diets rich in fast-foods and industrialized foods, in addition to low water intake.[2,3]Nephrolithiasis affects all ages, and during the first decade of life, the incidence is higher in boys, while girls are more likely to develop during the second decade of life.[1]

Studies with the adult population show a greater impact of this disease in western countries, to the detriment of eastern countries, with this incidence of 5-9% in Europe, 12-15% in North America, while in the east it is 5% - considering that the incidence of nephrolithiasis in children is 5 to 10% that estimated for adults.The fact that nephrolithiasis is endemic in some regions of the Middle East and North Africa is highlighted andmay affect up to 10-20% of the population, due to the higher occurrence of consanguinity, in

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addition to the high temperatures of these areas, which favor dehydration and deposition of the stones.[6]Populations that do not have the intestinal bacterium responsible for degrading oxalate, *Oxalobacter formigenes,* tend to develop absorptive hyperoxaluria, increasing the risk of developing oxalate stones, as occurs in Northern India, Ukraine, and the state of Florida in the United States.[7]Furthermore, there is a higher occurrence of urinary calculus in northeastern Thailand, due to the high incidence of renal tubular acidosis in this population.While in developed countries lithiasisdevelop mainly due to metabolic causes (up to 60%), infectious causes predominate in underdeveloped countries (up to 50%).This is due to better infection control, in addition to the early diagnosis and correction of urinary tract malformations in richer countries.[6]Thus, theaimofthisarticlewastoconduct a literaturereview, explainingtheetiologyandriskfactors,clinical presentation and diagnosis, treatmentandprevention,moreovercomplicationsandrelateddiseasesofnephrolithiasis in children.

II. Materials and Methods

This is a non-systematic literature review. The electronic databases Pubmed and Scielowere used. For the location of the articles, the terms "pediatric", "nephrolithiasis", "stones", "pediatric" and "children" were applied. Onlyarticles in Englishlanguagewassearched. For the selection of those that would be used in the study, those published between 2010 and 2020 were prioritized.Extraction from reports were made independently by two authors. In addition, the most relevant works were included, according to the respective databases. In all, 47 sources were selected and 39 used in this article.

Etiology and Risk Factors

The occurrence of nephrolithiasis involves genetic, dietary, socioeconomic, and constitutional factors.[2,3] As risk factors for the disease, there is low urinary volume, hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitraturia, cystinuria, crystallization-inhibiting protein deficiency, elevated or low urinary pH sepsis, or urinary infection by positive urease bacteria.[1]The composition of stones in children differs from those found in adults, and this is probably due to the greater association with the presence of metabolic abnormalities in pediatric patients.In these cases, the stones tend to have a mixed composition.[3]The most common calculations are calcium oxalate (up to 80%), followed by struvite (10-20%), calciumphosphate (5-10%), and uric acid alone (up to 5%).[5,8]Up to 22% of the calculations are of infectious origin.[4] Regarding age, it is observed that children under ten years are more prone to the formation of stones due to metabolic disorders, while those older than ten years often have low urinary volume.[1,4,9]In developed countries, the stones are mainly formed by calcium oxalate (60-90%) or calcium phosphate (10-20%), while in underdeveloped countries they tend to be uric acid or ammonium.[6]

Regarding genetic risk factors, in 30-80% of cases there is a positive family history, especially in endemic areas, mentioned above.[5]Studies indicate that mutations in specific genes are associated with lithiasis in the presence of idiopathic hypercalciuria, as a mutation in the gene encoding the receptor for vitamin D (VDR).[4,10]Genetic polymorphisms of this receptor also seem to be related to recurrent family urolithiasis, because the active form of vitamin D uses VDR to modulate the metabolism and transport of citrates, which may cause hypocitraturia.[14]

In addition, recurrent nephrolithiasis patients may have potentially protective proteins against the formation of stones in smaller amounts than the unaffected population. Among these substances, osteopontin, calgranulin, uromodulin and bikunin, which can be dosed from the patient's urine stand out.[4] In comparison with adults, children have more monogenic causes of nephrolithiasis.[3] Mutations isolated in at least 30 genes can cause monogenic forms of lithiasis,through autosomal recessive, autosomal dominant inheritances, or X-linked inheritances.[12]Among the monogenic causes are cystinuria, mutationsin hypoxanthine phosphoribosyltransferase, primary xanthinuria, andprimary hyperoxaluria.Between 5 and 10% of the stones in pediatric patients are secondary to cystinuria and are known at least two genes (SLC3A1 and SLC7A9) responsible for causing, through an autosomal recessive inheritance,this defect in thetransport of amino acids cysteine, lysine, arginine, and ornithine.[3]

There are also rare hereditarycauses of urinary calculus, such as tubulopathies or metabolic disorders, which cause early production of stones, with a high risk of progression to chronic kidney disease (CKD), such as adenine phosphoribosyltransferase(APRT),Dent's disease, familial hypomagnesemiawith hypercalciuria and nephrocalcinosis (FHHNC).The first is considered an innate error of metabolism, responsible for causing accumulation of 2,8-dihydroxyadenine, a substance responsible for the formation of stones and crystalline nephropathy. Dent's disease is characterized by hypercalciuria associated with low molecular weight proteinuria, leading to urolithiasisand/ornephrocalcinosis, and is caused by mutations in the CLCN5 and OCRL1 genes. FHHNC, on the other hand, results from mutations in the CLDN16 and CLDN19 genes.[13,15]

Hypercalciuriawas considered the main metabolic risk factor, followed by hypocitraturia, hyperuricosuria, and hyperoxaluria. However, recent studies indicate that hypocitraturia is responsible for 58-68% of cases of urolithiasis in childhood, thus constituting the most common risk factor. This data could be

explained by changes in dietary patterns, with excessive consumption of animal products, salt and sugar, in addition to reduced intake of vegetables, leading to reduced consumption of potassium and magnesium, and decreased urinary citrate.[8,16,17]

Dietary factors are closely related to metabolic abnormalities.Currently, there is an increase in sodium intake and reduction in water intake by the infant population.[3] The reduction of water in the body, and the consequent reduction of urine output, increases the relative supersaturation of urine and promotes the nucleation, growth, and aggregation of calcium oxalate and uric acid then favoring the formation of stones. In addition, excessive sodium intake is considered a risk factor for calculus since, during the resorption process along the nephron, there is a competition between sodium and calcium, thus increasing its excretion in the urine.Excessive consumption of animal protein and ketogenicdiet increases renal excretion of uric acid, calcium, and oxalate, in addition to promoting the reduction of urinary pH, which favors the precipitation of uric acid and calcium oxalate. In addition, there is a reduction in urinary levels of citrate, an inhibitor of the crystallization process.[3,18] Furthermore, the reduction of daily calcium intake causes an increase in serum calcitriol levels, increasing urinary calcium excretion.[5] Epidemiological studies suggest a correlation between Body Mass Index (BMI) and the risk for the formation of stones in children.[19]

As risk factors, it can also be mentioned prematurity, low birth weight, need for hospitalization in the neonatal intensive care unit (ICU) since it is related to the use of nephrotoxic drugs in immature kidneys.Also, use of drugs such as diuretics, anticonvulsants, and antibiotics. Inflammatory bowel diseases and short bowel syndrome, responsible for increasing intestinal absorption of oxalate and reducingcalcium. Neurological diseases that cause immobilizationin the bed or the wheelchair cause changes in calcium homeostasis, leading to bone resorption, hypercalciuria, and hyperphosphaturia, in addition to the possibility of reducing water intake. Finally, it is also possible to mention cystic fibrosis, hyperparathyroidism, hypervitaminosis D, malignancies, sarcoidosis, and other granulomatous diseases.[20,21]As for prematurity, 5-9% of patients born less than 32 weeks of age develop calculus. Furthermore, nutrition from formulated milk is also a riskfactor since they increase the excretion of solute by the kidneys. Premature infants receivingparenteral nutrition have high excretion of calcium and oxalate, associated with low citrate excretion, favoring calcium oxalate saturation. Studies have shown that the urine of preterm newborns has less ability to inhibit the formation of oxalate crystals when compared to the urine of full-term infants.[20,22]

In his study, Bozkurt suggests positive effects of breastfeeding on calculus disease already installed in pediatric patients. He concluded that the average duration of breast milk intake was longer in children without disease progression and in those with reduced size and/or the number of calculations. In addition, children who received only breast milk during the first six months of life required less treatment and showed less growth retardation.[23]

Clinical Presentation and Diagnosis

Regarding clinical manifestations, children tend to present more nonspecific symptoms. Pediatric patients may be asymptomatic and be diagnosed at random on routine examinations.[18]When present, the signs and symptoms are variable and depend on the age of the patient.[6]Adolescents and schoolchildren have a typical presentation, composed of flank pain, nausea, vomiting, dysuria, and hematuria. On the other hand, younger children have a more nonspecific clinical manifestation, such as diffuse abdominal pain associated with vomiting.Infants may present with irritability and frequent crying.[1,3]A typical presentation that can occur at all ages is gross non-glomerular hematuria and/or micro-hematuria, accompanied or not by flank sensitivity.Complete urinary retention associated with acute renal failure is a rare but possible event occurring as a result of urinary tract obstruction by calculus.[18]

It is essential to question the family history of urinary lithiasis since in 30-80% of cases there is a positive family history. Given the high clinical suspicion, complementary tests are needed.[3,5] Life habits such as diet, especially fluid intake, salt, and proteins, in addition to medications in use should be investigated. Furthermore, it is necessary to ascertain the presence or history of diseases that predispose to the formation of stones, such as chronic inflammatory bowel diseases, short bowel syndrome, vesicoureteral reflux, urinary tract obstruction, cystic fibrosis, and prolonged immobilization. Studies indicate that children with asthma are four times more likely to develop urinary lithiasis compared to the general population and, therefore, the presence of this disease, in the face of a suggestive condition, helps in clinical suspicion.[17]

Scientific evidence indicates the existence of children with occult urolithiasis, characterized by nonspecific complaints, such as abdominal pain, dysuria, and hematuria, which, when submitted to complementary tests, demonstrate abnormalities in the excretion of urinary solutes,despite not having identifiable ultrasound stones.It is therefore recommended to repeat ultrasound 1 to 2 years later, in children with occult urolithiasis, to detect possible stones.Marzuillo *et al*. recommends investigating urolithiasis and predisposing metabolic changes in: 1) Children with non-glomerular hematuria and/or dysuria, with no signs of inflammation in theexternal genitalia; 2) In children with acute/subacute abdominal pain (4 or fewer pain attacks

per month), recurrent abdominal pain, and family history of urolithiasis in 1st or 2nd-degree relatives; 3) Especially children under the age of eight, even if abdominal pain is diffuse; and 4) In children who have risk factors forurolithiasis.[21,24]

In younger children,recurrent urinary infections associated with the isolated presence of leukocytes in the urinary sedimentshould be considered as a high degree of suspicion for urolithiasis.[18]

Diagnosis is based on clinical history, associated with laboratory and imaging tests. Abdominal ultrasound is considered first-line examination in the face of clinical suspicion of urolithiasis, assisting in the evaluation of the presence, size, and location of the stone. Abdominal radiography can also be used, however not all compositions of stones can be visualized from it, besides requiring prior bowel preparation to promote better visualization. Non-contrast computed tomography (CT) is considered the gold standard since it has high sensitivity and specificity, however, it should be avoided by emitting ionizing radiation and requiring sedation. Thus, CT is reserved for special cases, such as surgical planning or when there is high clinical suspicion, when ultrasound does not evidence calculations.[3,18,21]

Even in cases where the diagnosis of calculus is evident, a thorough investigation of the condition is essential to identify potentially modifiable metabolic risk factors. Such a measure is necessary, considering the possibility of long-term renal damage, especially in cases of recurrent stones, presentation at an early age, and positive family history or consanguinity.[1,18]

Regarding laboratory tests, urinalysis provides information such as urine pH and its density. Urine analysis from polarized light microscopy allows identifying the chemical composition of the calculations, which can direct the investigation to rare causes, or indicate possible metabolic changes.[18]

24-hour urine analysis can also be performed in three samples taken at different times,which provides a qualitative and quantitative analysis of urinary solutes. In children who still use diapers, the number of urinary solutes can be approached from the solute/creatinine ratio. It is also necessary to check serum levels of creatinine, urea, uric acid, bicarbonate, and electrolytes. Depending on clinical suspicion, further tests may be needed, such as genetic analysis, for the rare diseases already mentioned.[17]

Approximately 40% ofurolithiasis patientshave idiopathic hypercalciuria, an inherited condition characterized by increased calcium excretion, despite a serum concentration within normal limits, and without identifiable metabolic causes. The most common calcium compound calculation is calcium oxalate.[11]

Hypocitraturia may be idiopathic due to metabolic acidosis, hypokalemia, inflammatory bowel disease, excessive consumption of animal protein, or secondary to the use of medications such as topiramate andacetazolamide. It is known that citrate inhibits the formation of stones, and therefore its decrease in urine predisposes to urolithiasis.[25,26]

Treatment and Prevention

Treatment is based on three pillars: symptom relief, removal of calculations (if necessary), and alteration of the patient's dietary-nutritional habits associated or not with drugs, to reduce risk factors for the formation of new stones.[1,2,3]

In pediatric patients, there are singularities regarding the development and presentation of the disease, being a sign of metabolic abnormality in 80% of cases, which, if not properly diagnosed and treated, can progress to long-term chronic kidney disease.[27]

In the absence of adequate treatment, the probability of recurrence is 80%, while the recurrence rate in the presence of optimal treatment is around 10-15%.[28]

Regarding the endurable measures, analgesia and hydration should be performed in all cases. Hydration reduces the urinary concentration of solutes, thus preventing the growth of existing calculations, besides favoring their expulsion. The total volume of liquid administered should be 70-100 ml/kg/day.[20]

Pharmacological or surgical treatment should be carried out in the following situations: pelvic or ureteral obstruction secondary to calculus, especiallyin the solitaryor transplanted kidney or in the presence of fever; refractory pain to the use of analgesics; and increased inflammatory index or sepsis. For the choice of treatment, it should consider variables such as stone localization, stone composition, the presence of obstruction, or infection.[18,29]

According to the American Urology Association (AUA),asymptomatic stones in pediatric patients should be followed up with imaging. The European Urology Association (AUE) recommends observing calculations smaller than 5mm.[30]Telli*et al.* recommends treating lower pole renal stones when they are larger than 7 mm in the presence of concomitant renal abnormalities or compound calculations of ammonium phosphate and magnesium(struvite) and cystine.[31]Asymptomatic stones greater than 20mm may be submitted to minimally invasive treatments, such as extracorporeal shockwave lithotripsy (LECO) and ureteroscopysince they have a rate without calculations, i.e., absence of residual stones or residual stones smaller than 4mm, 78%,lower thanpercutaneous nephrolithotomy.[32]

In the face of small calculations (<10mm), non-obstructive and located in the distal region of the ureter, that is, up to 2 cm above the ureterovesical junction, expulsive therapy with alpha-blockers or calcium channel blockers can be adopted. Such drugs act by relaxing the smooth musculature and favor the spontaneous elimination of calculus.[29]However, if after 4-6 weeks the calculation is not spontaneously eliminated and the patient continues to present pain episodes, procedures should be adopted for its removal.[33]

Infection-associated nephrolithiasis is considered a urological emergency, as it is associated with sepsis and increased mortality. In this context, it is necessary to immediately place the ureteral stent or percutaneous nephrostomy tube for drainage of the collecting system. Within three weeks of the patient should undergo ureteroscopy for removal of the calculus.[33]

LECO and ureteroscopy are considered, by the AUA, the first choice for the treatment of kidney and ureteral stones smaller than 20 mm. LECO is a good option in ureteral calculus or renal pelvis calculus smaller than 10 mm.[34] However, it is less effective in removing calcium oxalate monohydrate, cysteine, and localized calculations in the calyxes of the renal lower pole.[35] Among the possible complications of LECO, it can mention spinal subcapsular hematomas,liver hematomas, and splenic hematomas.[33]

Ureteroscopy was more powerful than LECO for distal ureteral stones greater than 10mm, and the rate of the former showed nocalculusof 78%,while the latter showed a rate of 45%.[36]In addition, the fragmentation of calculus greater than 10 mm by LECO may cause ureteral obstruction by a column of fragments, a situation called "stone street".[33]

Studies suggest that ureteroscopy may be effective in treating calculus larger than 20 mm, however it may be necessary to repeat the procedure. In this case, the rate without percutaneous nephrostomy calculus is higher, however, ureteroscopy has a lower risk of complications.[37]Possible complications of ureteroscopy include ureteral injury, ureteral stenosis, lower urinary tract symptoms, discomfort secondary to the use of ureteral stent, incomplete removal of calculus, and need for reapproach.[38]

Percutaneous nephrolithotomy (PCNL) is considered the first-line treatment for the treatment of stones larger than 20 mm.[30,32,34] This method presents, as possible complications, bleeding, pulmonary, colon, or intestine lesions, perforation of the renal pelvis, and lesion of the pelviureteric punction. Mini or micro PCNL is a technique that reduces renal trauma and bleeding complications.[33]

Open surgery to remove stones in children was replaced by minimally invasive methods and corresponds to only 1% of surgical interventions performed currently. It is a method used in special cases, such as in the presence of the associated structural problems standard, staghorn calculus, and large intra-bladder stones.[1,33]

Complications and Related Diseases

Children, in the presence of calculus, should be followed up on an outpatient basis, since the condition has the potential for complications, when not properly managed. Secondarily to nephrolithiasis, due to increased pressure inside the urinary tract, hydronephrosis can be developed, which is the dilation of the pyelocaliceal system. Mild to moderate dilations may regress spontaneously, however, large dilations may predispose the patient to urinary infections and injuries to the renal parenchyma.[1]Thus, Marra*et al* warns of the risk of progressive loss of renal function in the face of the occurrence of recurrent lithiasis.[18]

According to Jobs, lithiasis associated with hypercalciuria is associated with reduced bone density.[27]Kovacevic, through proteomic analysis, found a significant association betweenhypercalciuricandhypocitraturicnephrolithiasis and cardiovascular diseasesin children. The risk factors shared between the two diseases are endothelial dysfunction and atherosclerosis caused by abnormal coagulation, adept, transport disorder and lipid metabolism, oxidative stress, and inflammation.[39]

III. Conclusion

Due to the precariousness of eating habits and low water intake, the growth of nephrolithiasisin pediatric patients is unknown. Besides being an important cause of hospitalization, impacting the health system, it can present complications ranging from acute diseases,hydronephrosis, infection, and sepsis, to chronic, such as renal failure. Furthermore, evidence suggests a relationship between loss of bone mass and cardiovascular diseases with nephrolithiasis. It is necessary, therefore, appropriate diagnosis of the disease, through the knowledge of its typical and atypical manifestations, in order to treat the metabolic abnormalities of the patient and avoid future complications. Although the risk of recurrence of calculus is significant in children,appropriate treatment and clinical follow-up have been proven to reduce the likelihood of future recurrence as well as complications.

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